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Value of Information choices that influence estimates: A systematic review of prevailing considerations

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ABSTRACT

Background

Although Value of information (VOI) analyses are increasingly advocated and used for research prioritization and reimbursement decisions, the interpretation and usefulness of VOI outcomes depends critically on the underlying choices and assumptions used in the analysis. In this paper we present a structured overview of all items reported in literature to potentially influence VOI outcomes. Use of this overview increases awareness and transparency of choices and assumptions underpinning VOI outcomes.

Methods

A systematic literature review was performed to identify aspects of VOI analyses that were found to potentially influence VOI outcomes. Identified aspects were grouped, to develop a structured overview. Explanations were defined for all items included in the overview.

Results

We retrieved 687 unique papers, of which 71 original papers and 8 reviews were included. In the full text of these 79 papers 16 aspects were found that may influence VOI outcomes. These aspects related to the underlying evidence (bias, synthesis, heterogeneity, correlation), uncertainty (structural, future pricing), model (relevance, approach, population), choices in VOI calculation (estimation technique, implementation level, population size, perspective) and aspects specifically for assessing the value of future study designs (reversal costs, efficient estimator). These aspects were aggregated into 7 items to provide a structured overview.

Conclusion

The developed overview should increase awareness of key choices underlying VOI analysis, and facilitate structured reporting of such choices and interpretation of the ensuing VOI outcomes by researchers and policy makers. Use of this overview should improve prioritization and reimbursement decisions.

INTRODUCTION

Health economic modeling is rapidly becoming the standard for evaluating the expected cost-effectiveness of new healthcare interventions.(1) Characterizing the uncertainty in the expected costs and effects is important for determining: 1) the expected impact on health outcomes of incorrect decisions; 2) the potential value of additional evidence; and 3) whether access should be restricted (or delayed) until additional evidence is collected.(2) Value of Information (VOI) analysis can be used to quantify the expected value of eliminating all uncertainty, i.e., the expected value of perfect information (EVPI), or the expected value of eliminating uncertainty for specific parameters (or sets of parameters), i.e., the expected value of partial perfect information (EVPPPI). (3, 4) When compared to the costs of research, these VOI outcomes provide the maximum monetary value of additional research, which can be used as a criterion to support research prioritization decisions. VOI can also be used to establish optimal study design, sample size, and sequence of research by quantifying the expected value of sample information (EVSI) and the expected net benefit of sampling (ENBS).(5, 6)

The ISPOR-SMDM Modeling Good Research Practices Report on Model Parameter Estimation and Uncertainty Analysis (7) supports the use of VOI: “Perhaps the best measure of uncertainty surrounding a particular decision in cost-effectiveness analysis is the EVPI because this measure combines the probability of incorrect decision making with the consequential loss function.” VOI analysis is increasingly proposed and used in practice.(4, 8, 9) Recently, it was included in the revised Dutch pharmacoeconomic guidelines (10). Furthermore, it is becoming increasingly relevant in jurisdictions where decisions about new healthcare interventions are made close to license when the evidence base to support their use is most uncertain, for example, the European Medicines Agency recently introduced the “Adaptive Pathways” approach in an effort to provide patients with timely access to new medicine.(11, 12)

Choices for handling uncertainty in economic evaluations and VOI analysis have been described in the literature over the past decades. VOI analysis can capture all types of uncertainty, e.g., through

transformation into parameter uncertainty, however, in practice, VOI is often restricted to undertaking a limited subset of the underlying uncertainties.⁽¹³⁾ Consequently, it is important to assess the usefulness of the VOI outcomes reported for informing research and policy decisions. This requires a fully transparent description of the choices that are made during the analysis, which could potentially influence VOI outcomes. Some methodological VOI papers published to date indicate choices that could impact on results.⁽⁸⁾ Guidance on making these choices should come from best practice recommendations, however, currently even a comprehensive and structured overview of these choices is missing from the literature.

In this paper, we perform a systematic review to identify all aspects reported to (potentially) influence VOI outcomes, without ranking their importance. Based on the results, we develop a comprehensive and structured overview that can be used to assess the completeness and transparency of VOI studies to support research prioritization decisions.

METHODS

For the systematic review, we searched Pubmed database for records describing VOI. Given that typical journals publishing VOI papers are Medical Decision Making, Value in Health, Health Economics, and Pharmacoeconomics, searching Pubmed was deemed sufficiently comprehensive. We included all records in which VOI-related terms were presented in the publication title, abstract, or full text. No restrictions regarding type of records/publications, language, date of publication, study design, study outcomes, or funding, were applied. The search, last updated in April 27, 2017, is described in Appendix I.

After removing duplicate records, titles and abstracts were screened independently by two reviewers (JG and HK). Records were excluded if the publications a) did not address a healthcare-related topic, b) did not consider a cost-effectiveness or cost-utility analysis with associated VOI to inform research prioritization decisions, c) concerned an introductory text, tutorial, protocol or conference abstract, or d) described an application of VOI without the specific aim of addressing a methodological issue. Of the

remaining publications on the methodology of VOI, or providing a review of VOI, the full text was screened independently by two reviewers (JG and HK). Records were excluded based on full text if the corresponding publications: a) did not address any aspects concerning the methodology of VOI analysis, or b) compared VOI analysis with alternative approaches to research prioritization. Discordance between the reviewers was resolved by discussing the corresponding records until consensus was reached. From the full text of the included publications, VOI-related aspects potentially influencing VOI outcomes were extracted, independently and in duplicate (HK and JG). No selection was performed: all aspects (i.e. choices and considerations) mentioned in these publications as potentially being relevant to VOI analysis or VOI outcomes were extracted. To ensure completeness of the set of identified and extracted aspects, the full text of a random selection of 25% of publications reporting the application of VOI (but *not* specifically addressing VOI methodology) was also screened, to search for additional aspects. Aspects were not prioritized given the aim of this paper to provide a comprehensive overview of relevant aspects. During a final consensus meeting with all authors, aspects were grouped into broad and non-overlapping items, to reflect their relation and their link to more conceptual considerations. For example, all aspects that may influence VOI outcomes through determination of the number of patients who may benefit from additional research were grouped together. To obtain feedback on the comprehensiveness and structure of the overview from various stakeholders (e.g. researchers, clinicians, policy makers, patients and manufacturers), the overview was presented and discussed at an international conference.

RESULTS

Results of the literature search

The systematic review resulted in 687 records after excluding duplicates (Figure 1). Of these, 147 papers were unrelated to the healthcare context and 184 did not address VOI. In addition, 75 studies were excluded because they were introductory, tutorial or conference abstracts. A total of 174 papers were applications of VOI without specific focus on methodology performed in a healthcare context. Of the remaining 107 papers, the full text was assessed, and another 28 papers were excluded because they did not meet the inclusion criteria. Of the remaining 79 studies, 8 were review articles.

Figure 2 shows the cumulative number of applied, methodological and review studies on VOI in a healthcare context over the years. In the identified literature, the first applied VOI papers in healthcare appeared around 1998, and the proportion of methodological papers (~20%) appears to be stable over time since 2010. Overall, the number of papers on VOI has increased rapidly from 2005 to 2016. Previous VOI reviews have indicated that the level of reporting of methods used to conduct VOI analyses varies across the literature (14) and have suggested the need for standardization of reporting methods and results.(15) Furthermore, providing recommendations to decision makers on interpreting VOI outcomes (9) has been identified as an important area for future research.(8, 16) Two review articles assessed the usefulness of modeling and VOI to inform research prioritization decisions (17, 18) and one compared VOI approximation methods.(19)

Out of the 79 included papers all aspects that may influence VOI outcomes were extracted (16 aspects, Table 1). These aspects related to the underlying model (relevance, approach, population), evidence (bias, synthesis, heterogeneity, correlation), uncertainty (structural), choices in VOI calculation (estimation technique, implementation level, population size, perspective, future changes) and aspects specifically for EVSI and ENBS calculations (reversal costs, efficient estimator). Full text analysis of the additional 25% of applied VOI publications revealed no additional aspects. To create a structured overview with unique, non-overlapping items, all aspects related to the health economic model (i.e. 'modeling approach', 'model relevance', 'parameter estimation', 'heterogeneity between studies', 'quality of evidence', 'evidence synthesis', and '(structural) uncertainty') were clustered into one item (item #1; Table 2). The two aspects related to efficient estimation of either EVP(P)I or EVSI/ENBS were clustered together (#3), as were the aspects 'population who benefits from research' and 'eligible population' (#5). The aspects 'reversal costs' and 'research design' were clustered into one item concerning the proposed research portfolio; #7)). The other three aspects (i.e. 'perspective', 'implementation' and 'expected relevant future changes') were not clustered but remained separate items in the overview (#2, #4 and #6). Discussion of the overview at a conference did not result in additional aspects or items, or changes in structure. The resulting 7 items in the overview, ordered from the development of the model up to the potential EVSI/ENBS analysis, are described below.

Overview of items potentially influencing VOI outcomes

Item 1: Health economic model

VOI analysis is typically based on a health economic model that brings together all relevant evidence and reflects the uncertainty in the evidence. VOI analysis can only be as relevant, valid and useful as the underlying health economic model. Extensive good practices modeling guidelines exist to optimize and check the relevance and credibility of a model,(20) its validity,(21) the modeling approach,(1) how parameters are estimated and evidence is synthesized.(7) For optimal reporting of a health economic evaluation, the CHEERS checklist should be used.(22) Often different sources are available for a single parameter in the model. When synthesizing these sources, it is important that any heterogeneity between the studies is incorporated.(23-25)

The systematic examination and responsible reporting of uncertainty are hallmarks of good modeling practice.(7) When a model is used for estimating VOI outcomes, it is crucial that all existing uncertainty is identified and incorporated in the model, including structural uncertainty.(26-29)

Item 2: VOI perspective

VOI perspective is the viewpoint from which the costs and consequences of the existing uncertainty are evaluated. This perspective may differ from the relevant perspective of the economic evaluation. In many jurisdictions, a societal or payer perspective is most relevant because they will ultimately pay for the most cost-effective technology. However, if research is financed by a pharmaceutical company rather than public funding, it may be more relevant to calculate VOI from an industry perspective.(30)

Increasingly, research to reduce decision uncertainty regarding healthcare coverage is embedded in policies such as coverage with evidence development.(31) Here, industry generally pays for the research, but the value is used to inform a societal decision. Also, society or government pays for other costs resulting from the study, such as the costs of adverse effects or the costs of a strategy that, after the research period, turns out not to provide value for money but cannot be easily de-implemented because it is already used in practice.(32) In such cases, it may be informative to calculate the VOI from both

perspectives. If prices of the strategies are dependent on the results of further research, e.g., value-based pricing schemes, this affects the expected benefit of research from an industry perspective, and should be taken into account in VOI (see also item 6a).(30)

Item 3: VOI estimation

VOI outcomes can be derived using different methods, and the number of Monte Carlo samples used in the estimation process may impact on the accuracy of the outcomes.

Item 3a: Method of estimation or approximation: assumptions and bias

For interpretation and comparison of VOI outcomes, it is important to know which method of estimation has been used. Since the calculation of EVPPI and EVSI may be time consuming, approximation methods have been proposed to increase the efficiency of these calculations.(19, 33-54) However, these methods may not lead to equally accurate results and may have different conditions under which they provide valid estimates.(35)

EVSI is commonly estimated using a 2-level Monte Carlo procedure in which hypothetical results of future research are generated in an outer loop, and then, conditional on these, the parameters are updated and sampled in an inner loop. At each iteration of the inner loop, the model is evaluated. Since this method is computationally demanding, several methods have been proposed to calculate EVSI more efficiently. For example, a non-parametric regression-based method for estimating EVSI requiring only the probabilistic sensitivity analysis sample has been developed.(49)

Item 3b: Analysis of accuracy

Even if an appropriate estimation method has been used, the accuracy of VOI outcomes may depend on the number of samples used. Analyzing the convergence of estimates to ensure a threshold accuracy of EVPPI estimates fit for the specific purpose of the analysis is recommended.(33) A simple algorithm to estimate bias and confidence interval width for a specified number of samples can help determine how many outer and inner iterations are needed for a desired level of accuracy of EVPPI results.(38)

Item 4: Implementation

The current level of implementation (or uptake of a strategy in practice), as well as the expected change in implementation after research completes, may impact VOI outcomes.(29, 55-63)

Item 4a: Current level of implementation

Strategies that are deemed cost-effective do not automatically or immediately get implemented perfectly into practice.(64) Nonadherence by patients and healthcare professionals may be caused by multiple factors such as knowledge, attitude, or even chance. Less than perfect, or phased, implementation of cost-effective strategies reduces the efficiency of the healthcare system.(58) While this is commonly accepted, VOI generally assumes perfect implementation, i.e. if current evidence favors the new strategy, and no new evidence is sought or expected, all future patients will receive technology.(61) It is important to note that when the level of implementation (or noncompliance, nonadherence) is not explicitly specified or justified in VOI, one implicitly assumes that the cost-effective strategy is fully implemented in all eligible individuals, which is generally not realistic.

Item 4b: Expected change in implementation

VOI generally assumes immediate implementation of the results of future research.(61) However, in practice, the adoption of a new strategy requires time, and is dependent of the skills needed, the level of evidence, and the magnitude of the effect.(63) For example, there may be a minimum clinical difference required to change clinical practice.(60)

When the degree of implementation of decisions to adopt or reject a new strategy (partially) depends on the strength of the evidence provided by new research, this would increase the EVSI. Not assuming perfect implementation therefore increases the chance that the EVSI is positive, and that the optimal sample size for a new study is greater than 0.

As with the current level of implementation, when the expected changes in implementation are not explicitly defined and justified in VOI, one implicitly assumes that the cost-effective strategy is fully implemented immediately after additional research completes, independent of the magnitude of the effect or level of evidence.

Item 5: Population who benefits from research

VOI outcomes should be expressed for the eligible and affected population who can benefit from the results of research. Therefore, outcomes depend on the definition of this population, disease incidence and prevalence, the time horizon over which the additional evidence is expected to be useful, and the target jurisdiction(s).

Item 5a: Definition of the target population

It is important that the eligible population chosen for calculating VOI is justified. If the results of additional research only have consequences for a specific subgroup of patients, the net benefit of the research should be estimated for this subgroup.(65) In contrast, if the target indication is expected to be broadened in clinical practice, this should be taken into account. As VOI outcomes are a product of the VOI per patient and the size of the population that benefits from the research, under- or overestimating the eligible population will directly result in an under- or overestimation of VOI outcomes.(29)

Item 5b: Incidence/prevalence

Any estimate of the current and future benefits of research will be sensitive to assumptions about the future incidence of the disease.(66) Therefore, it is important to specify and justify the assumptions. If a strategy is used in all new patients, incidence estimates should be used. If the strategy can be used in all existing patients, e.g., a drug used in a chronic disease, the size of the eligible population is calculated combining the current prevalence of the disease with its future incidence. The VOI associated with future patients should be discounted appropriately, and the discount rate stated.

Item 5c: Time horizon over which produced evidence is expected to be useful

The chosen time horizon over which additional evidence is expected to be useful directly impacts on VOI outcomes through the corresponding size of the eligible population. In practice, arbitrary time horizons are commonly applied, e.g., 5 or 10 years, without justification. However, occasionally estimating the appropriate time horizon empirically may be feasible.(67, 68) Furthermore, the impact of uncertainty in

empirical estimates of VOI outcomes may be substantial.(68) Given the difficulties involved in empirically estimating the appropriate time horizon, use of a (set of) commonly applied time horizon(s) may at least allow comparison of VOI outcomes across studies.(69)

Item 5d: Target jurisdiction(s)

The target jurisdiction will determine the incidence and prevalence of disease (item 5b) and the size of the eligible population (item 5a), and thereby influence VOI outcomes. Although adoption decisions of new strategies are made in national or regional jurisdictions, performing additional research may actually have global value and impact.(44, 56, 59) Consequently, VOI outcomes estimated for particular jurisdictions are likely underestimations of the corresponding global VOI outcomes.(70) When VOI outcomes are provided for multiple jurisdictions, or for a global perspective rather than a national or regional jurisdiction this choice should be justified. Performing research across jurisdictions to improve the efficiency and value of collecting additional evidence is discussed in item 7a.

Item 6: Expected relevant future changes

VOI outcomes may depend on future changes over time that are expected to influence the price of the strategy and comparators, new evidence may become available, or new competitor technologies may enter the market.

Item 6a: Price changes

Although in many situations no evidence may be available on future price changes, occasionally there may be evidence that can be taken into account, e.g., price falls following patent expiry or increased uptake (item 4b).(62) Not explicitly modeling these changes effectively assumes that prices will not change over the time horizon. When prices do change this will affect VOI outcomes, and assumptions on the extent and timing of price changes will impact outcomes. (62, 68)

In addition to evidence from other ongoing studies, evidence from new research aimed at collecting additional evidence may affect the price of the strategies considered. For example, the ultimate price of a

drug may be set conditional on the effectiveness estimates from the new research through Value-based Pricing.(71) Accounting for this dependency may also impact VOI outcomes.(30)

Item 6b: Information changes

New information relevant to the health economic model may become available, e.g., from RCTs or observational studies reporting within the time horizon considered. In general, any new evidence becoming available from other, independent studies may affect the value of research. Not explicitly modeling changes in the availability of evidence effectively assumes that no new evidence will become available within the time horizon. When evidence on proposed, running, or (nearly) completed studies is available this can be formally modeled.(68)

Item 6c: Introduction of new technology

Every technology is liable to become obsolete and to be replaced (or modified) at some point in the future. When new competitors enter the market, and are included as comparators, this will impact the relative cost-effectiveness and uncertainty and, therefore, VOI outcomes. The nature of the new competitors may influence VOI outcomes, and can be classified as new technology with: 1) similar effect and price; 2) increased effectiveness and higher price; and 3) increased effectiveness and lower price.(68) Not explicitly modeling the introduction of new technology effectively assumes that this will not occur within the chosen time horizon.

Item 7: Proposed new study or research portfolio (if addressed)

When the collection of additional evidence is potentially worthwhile, researchers may focus on optimal single or multiple study design(s), the sequence of research needed, and the optimal methods for collecting the specific evidence. These proposed study designs should take proper account of all study costs and the costs associated with adoption decisions.

Item 7a: Optimal single study design

Although different study designs may be considered when contemplating the collection of additional evidence, research in this area has focused mainly on randomized controlled trials. In this commonly used design, decisions have to be made regarding, amongst others, the number of competing strategies to compare (study arms), the number of study participants (sample size), and the allocation of participants across strategies. Optimal choices for these decisions, in terms of maximum Expected Net Benefit of Sampling (ENBS) can be derived using dynamic programming.(45) Here, care should be taken not to exclude strategies from the analysis that are (extended) dominated in a deterministic cost-effectiveness analysis, as these may still be relevant when determining optimal future study designs.(45)

Optimizing study designs is also feasible from an industry perspective (see also item 2) where optimal study design may depend on the chance of regulatory approval, as a function of the strength of the evidence, as well as the design decisions.(72) Here, the value of additional evidence is generated by a potential increase in expected profit from increasing the chance of regulatory approval, and market share may depend on the size of the observed treatment effect. Regardless of the perspective, considering multi-stage studies instead of single-stage studies may result in substantial increases in expected net gain from research.(73, 74)

Finally, evidence collected within one jurisdiction may also be valuable in other jurisdictions, unless not transferable.(56, 70, 75) Consequently, study designs can be optimized not just within jurisdictions but also across jurisdictions.(70) In this case, optimal allocation of participants needs to be considered not only between trial arms but also between jurisdictions, accounting for potential freerider effects, spreading of fixed costs, and heterogeneity of evidence from multi-center multi-national studies.

Item 7b: Study costs and cost of reversing the decision

When assessing the net value of a new study or research portfolio the costs of evidence collection should always be taken into account. These costs comprise management costs and investigation costs, but also opportunity costs of participants included in the research.(76, 77) Randomizing participants, for example, ensures that a proportion of patients will not receive the strategy currently expected to have the highest net benefit. In addition, the time research takes to complete generally decreases the population that can ultimately benefit from the evidence collected within the decision time horizon (item 5c). Consequently,

the ENBS can be separated into 1) net benefits while the research is conducted, 2) net benefits once the research reports, 3) the costs of research, and 4) net benefits when the research is not conducted.(77) Uncertainty in the time until research reports can also be explicitly incorporated.(78) If irrecoverable costs (e.g. investment costs, costs of specific materials, equipment or training) are made, or if there are reversal costs (e.g. public health campaigns to reverse information flows) when the initial approval needs to be withdrawn, these should be accounted for in the VOI analysis.(76) Their impact may be reduced by risk sharing arrangements, in which the risk of reversal of a conditional approval decision is reduced by favorable price changes when, after additional research reports, the strategy considered would not be cost-effective.(75)

Item 7c: Optimal evidence collection method per (group of) parameters

When EVPPI results indicate the type of evidence that may be valuable, alternative methods of collecting the same evidence may exist. For example, 'gross costing' and 'micro costing' can be feasible and alternative methods of collecting evidence on costs.(79) Whenever there is a prior belief that one of the available methods measures the true quantity of interest, alternative methods provide approximations, and a relationship between the two is known or can be assumed, evidence collection can be optimized across collection methods.

Item 7d: Optimal research portfolio design

Instead of focusing on the potential worth of a single additional study, researchers can also investigate which research portfolio, that is, which sequence of studies potentially with different sizes and designs, would be optimal. While RCTs are attractive for some parameters due to the inherent minimization of bias, non-experimental studies may be useful for collecting evidence on, for example, complication risks and health-related quality of life measures. When multiple potential studies are not mutually exclusive, optimal evidence collection requires optimizing all studies in the research portfolio simultaneously rather than optimizing each study separately.(5) Mutually exclusive studies may be performed in sequence rather than concurrently, leading to the concept of conditional and sequential EVPPI.(6) Here, sequential

designs allow cancelling of research on additional parameters once research on (a) initially investigated parameter(s) reports. This may be valuable when costs of evidence collection varies substantially between (groups of) parameters, and the benefits of research on different parameters are interdependent on the value observed for them in new studies. However, optimizing any non-trivial portfolio of concurrent or sequential studies is only feasible when applying efficient (non-exhaustive) multivariate search algorithms.(5, 6)

DISCUSSION

In this systematic review we identified papers discussing VOI applications and methods, and found that methodological papers make up a relatively large part (~20%) of the identified published literature. From the identified methodological papers it was apparent that there are many choices in the modeling process and VOI analysis that can potentially influence the final VOI outcomes. This means that VOI outcomes from different studies cannot, in general, be directly compared, even though their unit of presentation (monetary value) suggests that a direct comparison is possible. We found that a structured overview containing 7 items, divided into sub items, provides useful insight into the completeness and transparency of VOI analyses. Use of this overview should increase transparency in the reporting of VOI outcomes and help policy makers to prioritize future research, while recognizing the usefulness of particular VOI outcomes, in addition to the actual numerical monetary outcome.

As the overview was based on a systematic review of existing literature in Pubmed papers focussing on VOI in journal not indexed in Pubmed were not included. Furthermore, the overview describes choices previously reported to be relevant. New thoughts not yet described in literature, such as for example related to sensitivity analyses around VOI outcomes, were therefore not included, but may be added in the future. Although the use of Delphi-panel techniques may have allowed to include such new thoughts, we chose to focus on those choices for which impact in VOI outcomes has actually been demonstrated,

for example in a case study. Discussion of the overview at an international conference did not reveal any missing or upcoming topics. In addition, we chose to focus on completeness of the overview rather than on (likely subjective) indications of relative importance of the items. Assessing differences in importance of items may be linked to assessing the strength of justifications of choices, accounting for best practice recommendations, for example, those forthcoming from the ISPOR Taskforce on VOI,(80) and is topic of future research.

Previous reviews already identified some of the identified items.(8, 16, 18) However, an exhaustive combination of all aspects into a structured overview, to standardize reporting, was still lacking, even though other reviews emphasized the importance of such standardization.(14, 15) As VOI analysis is typically performed using a health economic model, we also extracted aspects related to the use and synthesis of evidence and aspects related to the structure of the model. To reduce overlap with checklists that exist for the health economic model, we combined the model-related aspects into one item in the overview (item 1) and refer to existing checklists for the specific parts, such as relevance (20) and validity.(21) It should be emphasized that a good health economic model is a *necessary but not a sufficient condition* for the VOI outcomes to be valid and useful. When model checklists indicate that a particular model-based analysis may be acceptable, the completeness and transparency of subsequent VOI analyses still needs to be thoroughly checked, for example with the overview presented here.

VOI analysis can be a helpful guide to setting research priorities, for example in the context of conditional reimbursement schemes. In the United Kingdom, the Cancer Drugs Fund was recently reformed in order to allow drugs which are not (yet) shown to be cost-effective to be funded if there is a chance they might show cost-effectiveness after two years of evidence collection.(81) As such, there will be two years of evidence collection, with the risk of not having the possibility to reverse the decision even if the drug is ultimately not found (cost-)effective. However, the central role given to real world (observational) evidence is considered a major cause for concern.(82) VOI analysis could be used to determine whether data collection is worthwhile, and what the optimal design for collecting the evidence is. However, it is important that all assumptions are clear and justified where possible. Our overview offers guidance and can be used for this purpose. The structured overview contains some items that may be hard to judge by

reviewers and policy makers. This, however, clearly indicates the need for more transparent reporting of VOI analyses by researchers, but also for more knowledge and explicit deliberation on the validity of the underlying choices by reviewers and policy makers.

The need for standardizing VOI analysis and for improving its transparency is further demonstrated by the increasing use of, and demand for, VOI analysis as part of economic evaluations of strategies in healthcare. Two forthcoming ISPOR Taskforce reports also support the relevance of VOI analysis (report 1), and provide good practice recommendations for performing VOI analysis (report 2) and interpreting VOI outcomes (report 1&2).⁽⁸⁰⁾ The overview presented here is aligned with these reports and complements their good practice recommendations, which do not focus specifically on reporting, with an overview and explanation of relevant choices to report and motivate. For policy makers combining taskforce report 1 with this overview can enhance their appraisal of VOI outcomes whereas for VOI analysts combining taskforce report 2 with this overview can help explicating their approach and their choices.

Although VOI outcomes may seem comparable when expressed in the same currency, in practice they may be derived following very different analytical and modeling choices. Research prioritization based on simply comparing EVPI Euros or EVPI Dollars may therefore lead to incorrect funding decisions and should be avoided, particularly when the underlying analyses fail to capture all relevant uncertainty. With the structured overview presented here we aim to raise awareness of relevant choices that should be made explicit when reporting VOI outcomes. For example, not explicitly considering and defining the future level of implementation (after research completes) actually implies that immediate and perfect implementation is assumed. Use of the overview, for example as a checklist, also enhances the interpretation of VOI outcomes in general, by indicating which relevant choices have been made during the modeling and analysis, and to what extent these choices have been justified. This can help researchers and policy makers to improve research prioritization decisions by informing them on the completeness and transparency of VOI analyses, in addition to their actual numerical value.

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